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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,872	08/13/2001	Richard Kolesnick	6923-106	8412

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/928,872	KOLESNICK ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

--Th MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

THE REPLY FILED 09 December 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *09 December 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *See Continuation Sheet*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *1-3,5,7 and 9-13*.

   Claim(s) withdrawn from consideration: *None*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 3. Applicant's reply has overcome the following rejection(s): The enablement and written description rejections of Claims 1-3, 5, 7, 9-13 under 35 U.S.C. 112, first paragraph.

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 1-3, 5, 7 and 9-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe et al (Cell 74: 957-967, Sept 1993; PTO 1449) in view of Jarvis et al (Proc. Natl. Acad Sci USA: 91: 73-77, Jan 1994: PTO 1449), Cifone et al (EMBO J 14(23): 5859-68, 1995; PTO 1449) and US Pat No 5,773,278 (June 1998, PTO 892) or Horinouchi et al (Nature Genetics 10: 288-293, July 1995; PTO 1449) or Otterbach et al (Cell 81: 1053-61, June 1996; PTO 1449).

Lowe et al teaches a method for identifying compound which increases or decreases a cell's sensitivity to p53-mediated apoptosis comprising contacting p53 deficient cells (p53-/-) and p53 positive cells (p53+/- and p53+/+) with a test compound such as chemotherapeutic agents 5-Fluorouacil, etoposide, adriamycin, and sodium azide (See Table 1, page 958, Fig 5, in particular) to induce apoptosis (See Figs 2-6, page 965, Experimental procedure, in particular) wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis (See page 960, column 2, first full paragraph, Fig 6, in particular).

The claimed invention in claim 1 differs from the reference only by the recitation of contacting an acid sphingomyelinase-deficient cell and if the cell exposed to chemotherapeutic agent exhibits more severe apoptotic morphology than the control, the test compound represents a compound, which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

The claimed invention in claim 2 differs from the reference only by the recitation of contacting an acid sphingomyelinase-deficient cell and if the sphingomyelin is decrease while the level of ceramide increases in cell exposed to chemotherapeutic agent as compared to the control, the test compound represents a compound, which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

The claimed invention in claims 3 differs from the reference only by the recitation of the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for acid sphingomyelinase gene.

The claimed invention in claims 5 differs from the reference only by the recitation of the cell exhibiting acid sphingomyelinase activity with a test compound, exposing said cells to a chemotherapeutic stress stimulus, comparing the levels of sphingomyelin and ceramide and if the sphingomyelin level is greater while ceramide level is less than the control, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

The claimed invention in claims 7 differs from the reference only by the recitation of the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

The claimed invention in claims 9 differs from the reference only by the recitation of the apoptotic morphology comprises cellular condensation, nuclear condensation and zeiosis.

The claimed invention in claims 10 and 11 differs from the reference only by the recitation of the acid sphingomyelinase-deficient cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

The claimed invention in claims 12 differs from the reference only by the recitation of the transgenic cells that are deficient in endogenous acid sphingomyelinase gene activity and contain a functional human acid sphingomyelinase gene.

The claimed invention in claims 13 differs from the reference only by the recitation of the cells are genetically engineered cells that exhibit greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type.

Jarvis et al teach when cells such as HL60 and U937 that exhibiting acid sphingomyelinase activity are exposed to various chemotherapeutics stress such as sphingomyelinase and C8ceramide, the cells undergo apoptosis (See entire document, Figs 1, 3 and 6, in particular). Jarvis et al teach how to determine the morphological features of apoptosis such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular).

Cifone et al teach when cells such as HuT78 that exhibits acid sphingomyelinase activity are exposed to chemotherapeutics stress stimulus such as crosslinking Fas receptor using anti-Fas antibody or TNF, apoptotic cell death results. This is associated with a decrease in the level of sphingomyelin (breakdown) with a concomitant increase in the level of ceramide (generation) (See Figs 2-4, 7, page 5865-5866, Materials and methods, in particular). Cifone et al teach how to measure the levels of ceramide and sphingomyelin (See page 5866, column 1, in particular). Cifone et al teach that it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis such as measuring the levels of ceramide and sphingomyelinase activity (See page 5865, column 2, Biological implications, in particular).

The '278 patent teaches acid sphingomyelinase deficient cell and cell line such as fibroblast or lymphoblasts generated from Niemann-Pick disease (NPD) patient and transgenic mice overexpressing the human acid sphingomyelinase gene (See column 27, lines 61-67, column 34, lines 17-30, in particular). The '278 patent teaches nucleotide encoding for human acid sphingomyelinase (ASM) is useful for engineering transgenic mice and cell lines overexpressing the human ASM for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular).

Horinouchi et al teach acid sphingomyelinase deficient mice as a model for type A and B human Niemann-Pick disease (See entire document, Methods, in particular).

Otterbach et al teach acid sphingomyelinase deficient mice as a model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the p53 deficient cells for a method for identifying compound which increase or decrease a cell's sensitivity to apoptosis to p53 as taught by Lowe et al for the acid sphingomyelinase deficient cells wherein the cells are part of the cell lines or genetically engineered transgenic mouse or cell lines expressing or overexpressing the human ASM as taught by the '278 patent or the genetically engineered mice deficient for the acid sphingomyelinase as taught by Horinouchi et al or Otterbach et al for a method for identifying compound which increases or decreases a cell's sensitivity to sphingomyelinase-related apoptosis as taught by Cifone et al and Jarvis et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Jarvis et al

teach acid sphingomyelinase induces cell death by apoptosis in cells exhibiting acid sphingomyelinase activity (See entire document, Figs 1, 3 and 6, in particular). Cifone et al teach that it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular). The '278 patent teaches that Niemann-Pick disease (NPD) is associated with acid sphingomyelinase deficiency and human acid sphingomyelinase (ASM) transgenic mice and cell lines overexpressing the human ASM is useful for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular). Horinouchi et al teach acid sphingomyelinase deficient mice as a model for type A and B human Niemann-Pick disease (See entire document, Methods, in particular). Otterbach et al teach acid sphingomyelinase deficient mice is a useful model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular).

Applicants' arguments filed 12/9/02 have been fully considered but are not found persuasive.
Applicants' position is that (1) Lowe does not teach methods to identify any compounds, Lowe teahes p53, not any test compounds modulates a cell's sensitivity to chemotherapeutic agent. By contrast, the test compounds are selected based on their ability to affect the acid sphingomyelinase pathway; (2) Javis et al teach neutral sphinogmyelinase and not acid sphingomyelinase in the sphingomyelinase pathway; (3) Clifone et al discusses the potential role of acidic sphingomyelinase in apoptosis, the role of acidic sphingomyelinase in apoptosis was controversal and it was generally accepted that acid sphingomyelinase was not involved in apoptosis. (4) Schuman et al discloses the full length human acid sphingomyelinase nucleotide and protein sequences and methods of producing transgenic mice that may serve as models for Niemann-Pick Disease. (4) Otterbach teaches how to produce transgenic ASM deficient mice. However, compound identification methods are not taught in any of these disclosures. (5) There is no suggestion or motivation to modify the references. (6) There is no reasonable expectation of success. (7) Not all the claims limitations are taught or suggested by the cited references. Specifically, the use of test compounds to identify a compound that modulates an acid sphingomyelinase apoptotic pathway is not taught or suggested by any of the cited references.

In response to applicant's arguments, Lowe et al teach a method for identifying compound which increases or decreases a cell's sensitivity to p53-mediated apoptosis comprising contacting p53 deficient cells (p53-/-) and p53 positive cells (p53+/- and p53+/+) with a test compound such as chemotherapeutic agents 5-Fluorouacil, etoposide, adriamycin, and sodium azide (See Table 1, page 958, Fig 5, in particular) to induce apoptosis (See Figs 2-6, page 965, Experimental procedure, in particular) wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis (See page 960, column 2, first full paragraph, Fig 6, in particular). Lowe further teach that a cell's sensitivity to chemotherapeutic agent depends on the presence or absence of p53 as pointed by Applicant. Further, Cifone et al teach when cells such as HuT78 that exhibits acid sphingomyelinase activity are exposed to chemotherapeutics stress stimulus such as crosslinking Fas receptor using anti-Fas antibody or TNF, apoptotic cell death results. Cifone et al implicates acid sphingomyelinase might play a role in apoptosis. Jarvis et al teach how to determine the morphological features of apoptosis such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular). Jarvis et al further teach when cells such as HL60 and U937 that exhibiting acid sphingomyelinase activity are exposed to various chemotherapeutics stress such as sphingomyelinase and C8ceramide, the cells undergo apoptosis (See entire document, Figs 1, 3 and 6, in particular). Applicant's contention that the art made of record is devoid of any teaching or suggestion that would impel the ordinary artisan to modify the teachings of the cited references to arrive at the claimed invention is acknowledged. However, for the reasons of record and addressed herein, the combination of references do provide clear motivation and expectation of success in methods for identifying compounds that is sensitive to acid sphingomyelinase-related apoptosis using acid sphingomyelinase deficient cells expososed to chemotherapeutic agents. Further it is noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine , 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones , 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The recitation of the use of test compound to identify a compound that modulates an acid sphingomyelinase apoptotic pathway is an obvious variation of the method of Lowe et al by exposing more than one chemotherapeutic agents to acid sphingomyelinase deficiency cells as taught by Horinouchi et al or Horinouchi et al and acid sphingomyelinase containing cells as taugth by Cifone et al (as control) and ask whether the combination of compounds increase or decrease apoptosis by measuring the levels of apoptosis and sphingomyelinase activity as taught by Jarvis et al.

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